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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,081	04/01/2004	David B. Rozema	Mirus.035.02.1	8619

25032 7590 07/24/2008

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
07/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,081	ROZEMA ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,22,23 and 27-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,22,23 and 27-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 4/28/2008, in which claims 19, 23 and 27 were amended. Currently, claims 19, 22-23 and 27-32 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group II without traverse in the reply filed on 9/18/2006. Currently, claims 19, 22, 23 and 27-32 are under consideration.

Response to Arguments - 35 USC § 112

The rejection of claim 23 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claim in the reply filed 4/28/2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 22, 23 and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1, cited in a prior action; see the entire reference) in view of Richardson et al (Biomacromolecules, Vol. 2, pages 1023-1028, 2001; see the entire reference). This is a new rejection, necessitated by the amendment to the claims to require the polyamine to be capable of causing liposome leakage.

Wolff teaches a method for delivering a polynucleotide to the cytoplasm of a cell, comprising the steps of (i) condensing the polynucleotide with a cation to form a condensed polynucleotide binary complex (polycation/nucleic acid complex), (ii) associating the binary complex with a polyanion (polyanion/polycation/nucleic acid complex), and (iii) delivering the ternary complex to the cell where it is endocytosed (e.g., pages 16-19). Wolff teaches that the polyanion may be cleavable by the addition of a polyion cleavable in the side chain, where acids, esters and amides of carboxylic acid derivatives are reacted with amines (e.g., paragraph bridging pages 21-22). Specifically, Wolff teaches the reaction of dimethylmaleyl acid, a disubstituted maleic anhydride derivative, with an amine group on the polyion (e.g., paragraph bridging pages 11-12; paragraph bridging pages 21-22). Wolff teaches the reaction of the maleic anhydride derivative with the amine of the polymer to form a labile bond (e.g., paragraph bridging pages 21-22). The labile bond taught by Wolff et al is a pH-labile bond, as the

specification teaches that the reaction of a maleic anhydride derivative with an amine results in the formation of a pH-labile bond (e.g., page 6, lines 14-15; Figure 2). Specific amines taught by Wolff et al are poly-L-lysine, spermine, spermidine, N,N'-bis(2-aminoethyl)-1,3-propanediamine (AEPD), and 3,3'-Diamino-N,N-dimethyldiproplyammonium bromide (e.g., 6, lines 14-20; page 10, lines 13-19). Further, Wolff teaches that polyethylenimine (PEI, a polyamine) is capable of disrupting endosomal function without additional treatments. Moreover, Wolff teaches that agents that disrupt the endosome can be used to increase the delivery of the polynucleotide to certain parts of the cell (e.g., page 11, lines 18-21). Wolff teaches the formation of polymers containing two to more than 80 monomers, which would result in a molecular weight of at least 10,000 Daltons (e.g., paragraph bridging pages 6-7). Wolff teaches that the particles formed by the method are salt stable nanoparticles (e.g., Example 8; Table 3).

Wolff does not specifically teach the addition of dimethylmaleyl acid to a polyamine capable of causing liposome leakage.

Richardson et al teach a new family of polymeric drug carriers based on synthetic, linear poly(amdidoamine) (PAA) polymers (e.g., page 1023, paragraph bridging columns; Table 1). Richardson et al teach that amphoteric PAAs undergo a change in tertiary conformation in response to a drop in pH over the physiologically relevant pH range of 7.4-5.5, which confers the ability to selectively damage biological membranes at low pH (e.g., 1023, paragraph bridging columns). Thus, the PAA polymers would be capable of causing liposome lysis at low pH. Richardson et al teach analogues of PAA polymers with an average molecular weight greater than 10,000 Daltons (e.g., page 1023, right column; Table 1). The PAAs were able to promote transfection of HEPG2 cells with plasmid DNA; ISA 23 was as effective as PEI and LipofectIN,

and ISA 22 and ISA 23 were more effective than LipofectACE (e.g., page 1027, right column, full paragraph). Unlike PEI and poly-L-lysine, PAAs show minimal toxicity (e.g., paragraph bridging pages 1027-1028).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide of Wolff to include the reaction of dimethylmaleyl acid with amino groups of the PAA polymers taught by Richardson et al, because Wolff teaches it is within the skill of the art to perform the reaction and teach the use polyethylenimine (PEI) in transfection methods, and Richardson et al teach that PAAs perform as well as PEI in the transfection of cultured HEPG2 cells. The addition of dimethylamaleyl acid to the PAA would result in the formation of a negatively charged reversibly inhibited membrane active polymer, which results in the formation of a ternary complex with a net negative charge.

One would have been motivated to make such a modification in order to receive the expected benefit of increasing delivery to the cells through disruption of the endosome as taught by Wolff using a polymer that is less toxic to cells as taught by Richardson et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1, cited in a prior action; see the entire reference) in view of Richardson et al (Biomacromolecules, Vol. 2, pages 1023-1028, 2001; see the entire reference) as applied to claims 19, 22, 23 and 29-32 above, and further in view of Wolff (WO 00/75164 A1, cited in a

prior action; see the entire reference). This is a new rejection, necessitated by the amendment to the claims to require the polyamine to be capable of causing liposome leakage.

The combined teachings of Wolff (WO 00/03694) and Richardson et al are described above and applied as before.

Wolff (WO 00/03694) and Richardson et al do not teach the method where the disubstituted maleic anhydride derivative is carboxydimethylmaleic anhydride.

Wolff (WO 00/75164) teaches the synthesis of 2-propionic-3-methylmaleic anhydride (carboxydimethylmaleic anhydride or C-DM) and the reaction of this compound to polyamines for use in the transfection of cells with a polynucleotide (e.g., page 19, lines 20-25; page 21, line 15 to page 22, line 30; page 23, lines 21-25; page 63, lines 1-18; page 65, lines 8-14; page 66, lines 21-27; Example 7). Wolff teaches that the addition of 2,3-dimethylmaleamic acid to a polyamine increases the transfection efficiency as compared to succinimic modified polyamine (e.g., page 78, Table). Wolff teaches that 2-propionic-3-methylmaleamic modified polyamine further increases transcription efficiency as compared to 2,3-dimethylmaleamic acid under the same conditions (e.g. page 78, Table). Wolff teaches that the bond between the maleic acid anydride derivative and the polyamine is a pH-labile bond, which would be cleaved in the endosome (e.g., paragraph bridging pages 20-21; paragraph bridging pages 22-23; page 24, lines 5-17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the transfection method of Wolff (WO 00/03694) and Richardson et al to replace the dimethylmaleyl acid with the carboxydimethylmaleic anhydride taught by Wolff (WO 00/75164) because both Wolff references teach it is within the ordinary skill in the art to

react a maleic acid anhydride derivative with a polyamine for use in transfection of cells with a polynucleotide.

One would have been motivated to make such a modification in order to receive the expected benefit of increased transfection efficiency as taught by Wolff (WO 00/75164). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 19, 22, 23 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1, cited in a prior action; see the entire reference) in view of Rittner et al (US Patent Application Publication No. 2002/0055174 A1; see the entire reference). This is a new rejection, necessitated by the amendment to the claims to require the polyamine to be capable of causing liposome leakage.

Wolff teaches a method for delivering a polynucleotide to the cytoplasm of a cell, comprising the steps of (i) condensing the polynucleotide with a cation to form a condensed polynucleotide binary complex (polycation/nucleic acid complex), (ii) associating the binary complex with a polyanion (polyanion/polycation/nucleic acid complex), and (iii) delivering the ternary complex to the cell where it is endocytosed (e.g., pages 16-19). Wolff teaches that the polyanion may be cleavable by the addition of a polyion cleavable in the side chain, where acids, esters and amides of carboxylic acid derivatives are reacted with amines (e.g., paragraph bridging pages 21-22). Specifically, Wolff teaches the reaction of dimethylmaleyl acid, a disubstituted maleic anhydride derivative, with an amine group on the polyion (e.g., paragraph

bridging pages 11-12; paragraph bridging pages 21-22). Wolff teaches the reaction of the maleic anhydride derivative with the amine of the polymer to form a labile bond (e.g., paragraph bridging pages 21-22). The labile bond taught by Wolff et al is a pH-labile bond, as the specification teaches that the reaction of a maleic anhydride derivative with an amine results in the formation of a pH-labile bond (e.g., page 6, lines 14-15; Figure 2). Specific amines taught by Wolff et al are poly-L-lysine, spermine, spermidine, N,N'-bis(2-aminoethyl)-1,3-propanediamine (AEPD), and 3,3'-Diamino-N,N-dimethyldiproplyammonium bromide (e.g., 6, lines 14-20; page 10, lines 13-19). Further, Wolff teaches that polyethylenimine (PEI, a polyamine) is capable of disrupting endosomal function without additional treatments. Moreover, Wolff teaches that agents that disrupt the endosome can be used to increase the delivery of the polynucleotide to certain parts of the cell (e.g., page 11, lines 18-21). Wolff teaches the formation of polymers containing two to more than 80 monomers, which would result in a molecular weight of at least 10,000 Daltons (e.g., paragraph bridging pages 6-7). Wolff teaches that the particles formed by the method are salt stable nanoparticles (e.g., Example 8; Table 3).

Wolff does not specifically teach the addition of dimethylmaleyl acid to a polyamine capable of causing liposome leakage.

Rittner et al teach cationic peptides, comprising multiple amine groups, which are capable of causing membrane disruption, including leaking endosomal, lysosomal or synthetic liposomal membranes (e.g., paragraphs [0017]-[0051]). Rittner et al teach a complex for transferring an anionic substance of interest into a cell comprising: at least one peptide of the invention, and at least one anionic substance such as a polynucleotide (e.g., paragraphs [0052]-[0056]). Rittner et al teach that the peptides of the invention, such as ppTG1, cause membrane

disruption in a liposomal leakage assay with POPC liposomes (e.g., paragraphs [0205]-[0208]; Table 1). Using ppTG1 to transfect plasmid DNA into 293-EBNA1 cells resulted in higher efficiency as compared to Lipofectin or PEI (e.g., paragraph [0213]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide of Wolff to include the reaction of dimethylmaleyl acid with amino groups of the peptides taught by Rittner et al, because Wolff teaches it is within the skill of the art to perform the reaction and teach the use polyethylenimine (PEI) in transfection methods, and Rittner et al teach that the disclosed peptides perform better than PEI in the transfection of cultured 293-EBNA1 cells. The addition of dimethylamaleyl acid to the peptides would result in the formation of a negatively charged reversibly inhibited membrane active polymer, which results in the formation of a ternary complex with a net negative charge.

One would have been motivated to make such a modification in order to receive the expected benefit of increasing delivery to the cells through disruption of the endosome as taught by Wolff using a polymer that allows for more efficient delivery of the polynucleotide as taught by Rittner et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1, cited in a prior action; see the entire reference) in view of Rittner et al (US Patent Application Publication No. 2002/0055174 A1; see the entire reference) as applied to

claims 19, 22, 23 and 30-32 above, and further in view of Wolff (WO 00/75164 A1, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment to the claims to require the polyamine to be capable of causing liposome leakage.

The combined teachings of Wolff (WO 00/03694) and Rittner et al are described above and applied as before.

Wolff (WO 00/03694) and Rittner et al do not teach the method where the disubstituted maleic anhydride derivative is carboxydimethylmaleic anhydride.

Wolff (WO 00/75164) teaches the synthesis of 2-propionic-3-methylmaleic anhydride (carboxydimethylmaleic anhydride or C-DM) and the reaction of this compound to polyamines for use in the transfection of cells with a polynucleotide (e.g., page 19, lines 20-25; page 21, line 15 to page 22, line 30; page 23, lines 21-25; page 63, lines 1-18; page 65, lines 8-14; page 66, lines 21-27; Example 7). Wolff teaches that the addition of 2,3-dimethylmaleamic acid to a polyamine increases the transfection efficiency as compared to succinimic modified polyamine (e.g., page 78, Table). Wolff teaches that 2-propionic-3-methylmaleamic modified polyamine further increases transcription efficiency as compared to 2,3-dimethylmaleamic acid under the same conditions (e.g. page 78, Table). Wolff teaches that the bond between the maleic acid anydride derivative and the polyamine is a pH-labile bond, which would be cleaved in the endosome (e.g., paragraph bridging pages 20-21; paragraph bridging pages 22-23; page 24, lines 5-17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the transfection method of Wolff (WO 00/03694) and Rittner et al to replace the dimethylmaleyl acid with the carboxydimethylmaleic anhydride taught by Wolff (WO

00/75164) because both Wolff references teach it is within the ordinary skill in the art to react a maleic acid anhydride derivative with a polyamine for use in transfection of cells with a polynucleotide.

One would have been motivated to make such a modification in order to receive the expected benefit of increased transfection efficiency as taught by Wolff (WO 00/75164). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claims 19, 22, 23 and 29-32 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1) has been withdrawn in view of Applicant's amendment to the claims, in the reply filed 4/28/2008, to require the polyamine to be capable of causing liposome leakage. The declaration of Dr. Rozema provides evidence that PEI does not cause liposome leakage.

The rejection of claims 27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1) in view of Wolff (WO 00/75164 A1) has been withdrawn in view of Applicant's amendment to the claims, in the reply filed 4/28/2008, to require the polyamine to be capable of causing liposome leakage. The declaration of Dr. Rozema provides evidence that PEI does not cause liposome leakage.

Response to Amendment – Declaration of Dr. Rozema

The declaration under 37 CFR 1.132 filed 4/28/2008 is sufficient to overcome the rejection of claims 19, 22, 23 and 27-32 based upon the Wolff (WO 00/75164 A1) reference applied under 35 U.S.C. 103(a).

The declaration of Dr. Rozema provides evidence that PEI does not cause liposome leakage.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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